

## PATENT SPECIFICATION

(11) 1234058

1234058

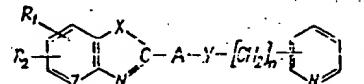
NO DRAWINGS

(21) Application No. 49798/68 (22) Filed 21 Oct. 1968  
 (45) Complete Specification published 3 June 1971  
 (51) International Classification C 07 d 31/28, 31/50, 49/38, 57/04, 91/44  
 (52) Index at acceptance  
 C2C 173—197—288 183—199—283 1M1C3 213 215  
 246 247 250 251 252 25Y 28X 29X 29Y 30Y  
 332 373 37Y 3A13C10B 3A13C10D 3A13C5  
 5A4 5E2 614 671 790 791 79Y RV

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 AZOLE DERIVATIVES

(71) We, EGYESULT GYOGYSZER ES  
 TAPSZERGYAR, a Hungarian Body Corporate  
 of 30—38, Keresztrui ut, Budapest X,  
 Hungary, do hereby declare the invention, for  
 which we pray that a patent may be granted  
 to us, and the method by which it is to be  
 performed, to be particularly described in and  
 by the following statement:—

This invention relates to new azole derivatives.  
 More particularly, it is concerned with  
 new pyridylalkyloxy and pyridylalkylthio azole  
 derivatives having the general formula I



and their physiologically compatible acid addition salts and quaternary ammonium derivatives. In the general formula I

A stands for an alkylene group containing 1—5 carbon atoms or a valence bond;

X stands for an —NH group or an oxygen or sulphur atom;

Y stands for a sulphur or oxygen atom;

Z stands for a —CH— group or a nitrogen atom;

R<sub>1</sub> stands for a hydrogen atom or a methyl group;

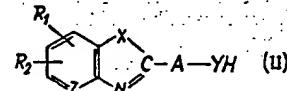
R<sub>2</sub> stands for a hydrogen or chlorine atom, or a —NO<sub>2</sub> or —CH<sub>3</sub> group; and

n is an integer from 1 to 3.

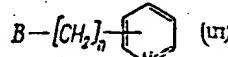
The compounds of the general formula I possess valuable biological properties. They show tuberculostatic and other bacteriostatic activity, in addition to insecticidal, fungicidal, antiviral, antihelmintic and antiinflammatory activities.

The new compounds having the general formula I can conveniently be prepared by

reacting an azole derivative having the general formula II



wherein A, R<sub>1</sub>, R<sub>2</sub>, X, Y and Z have the same meanings as above, with a pyridine derivative having the general formula III



wherein B stands for an —NH<sub>2</sub> group or a halogen atom, and n has the same meaning as above, or with a salt thereof. 2-(2-aminoethyl)pyridine is a preferred compound of formula III.

This reaction is preferably carried out at a temperature of from 100 to 150°C.

The halogen alkyl pyridines having the general formula III or the salts thereof are preferably reacted in an amount equivalent to that of the azole derivative having the general formula II. The reaction is carried out preferably in the presence of an acid-binding agent, especially sodium hydroxide.

As indicated above, the compounds according to the invention possess basic properties and form acid addition salts and quaternary ammonium derivatives.

If it is desired to obtain the acid addition salt from the free base, the salt can be prepared by reacting the free base with a corresponding inorganic or organic acid, such as hydrochloric, hydrobromic, sulphuric, phosphoric, tartaric, lactic, acetic, p-toluene-

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sulphonic, mandelic, salicylic, citric and other physiologically compatible acids, preferably in the presence of a suitable solvent permitting isolation of the salt.

5 The quaternary ammonium derivatives can be prepared by reacting the free base with an alkyl halide, preferably in the presence of an inert solvent.

10 On the other hand, when it is desired to convert the acid addition salt or the quaternary ammonium derivative to the free base, this can be accomplished by dissolving the salt in a suitable solvent, neutralizing the solution with a basic material, such as sodium

15 hydroxide, and isolating the desired base by extraction or other suitable means.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one of the compounds having the general formula I and/or their physiologically compatible acid addition salts and quaternary ammonium derivatives, in admixture with suitable carriers and/or excipients.

20 Said pharmaceutical compositions may be solid (e.g. tablets, pills, coated pills, suppositories, capsules) or liquid (such as solutions, suspensions, emulsions, or injectable preparations). These preparations may be suitable for oral, rectal, or parenteral administration.

25 The carriers may be conventional organic or inorganic substances, such as starch, magnesium stearate, talc, stearine, water, polyalkylene glycols and magnesium carbonate.

30 The pharmaceutical compositions may contain additives such as emulsifying, stabilizing, disintegrating and wetting agents.

35 The preparations may comprise in addition to the compounds of the general formula I one or more other therapeutically active compounds.

40 The pharmaceutical compositions according to the present invention may be prepared by the usual methods of the pharmaceutical industry known *per se*, by admixing the active ingredient with suitable solid or liquid organic or inorganic pharmaceutical carriers and/or excipients and, if desired, with other therapeutically active compounds.

45 The new compounds according to the invention and their methods of preparation are further illustrated by the aid of the following Examples.

EXAMPLE 1

55 30 g. (0.2 moles) of 2-mercaptopbenzimidazole and 24.4 g. (0.2 moles) of 2-(2-aminoethyl)-pyridine are heated at 150°C on a metal bath until the intensive evolution of ammonia gas ceases (about 3 hours).

60 After cooling, the product is dissolved in ethanol or acetone and the solution is decolourised with charcoal. The solution is then diluted with water, whereupon 2-( $\beta$ -pyrid-2-ylethylthio)benzimidazole separates in crystalline form, with a yield of 80%.

65 If an analytical sample is crystallized from 50% ethanol, the pure base is obtained with a melting point of 75-77°C.

70 If gaseous hydrochloric acid is introduced into the acetone solution of the base so obtained, or the solution is acidified with a 1:1 mixture of ethanol and 38% HCl, then the white crystalline dihydrochloride of the amine separates, and has a melting point of 198-201°C.

75 If the acetone solution of the base, obtained as described above, is refluxed with methyl iodide, the yellowish white quaternary dimethyliodide salt separates, after cooling, and has a melting point of 246-248°C.

EXAMPLE 2

80 16.7 g. (0.1 moles) of 2-mercaptopbenzothiazole are dissolved in 200 ml. of ethanol, whereafter 16.4 g. (0.1 moles) of 4-chloromethyl pyridine hydrochloride and 8 g. (0.2 moles) of NaOH dissolved in a small amount of water are added to the solution.

85 The reaction mixture is refluxed for two hours and sodium chloride (11 g.) is then separated by filtration. The filtrate is evaporated and the residue crystallized from aqueous acetone, to give solid 2-(pyrid-4-ylmethylthio)benzothiazole. Yield: 75%; m.p.: 85-87°C.

90 If the acetone solution of the base so obtained is acidified with hydrochloric acid, the yellowish-white dihydrochloride separates; m.p.: 174-177°C.

95 If the acetone solution of the base is refluxed with methyl iodide and is then diluted with ether, the quaternary monomethyl iodide salt is precipitated in the form of yellow crystals having a melting point of 150-152°C.

100 The compounds listed in the following Table have been prepared by the methods described in Examples 1 and 2.

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Ex. No.	R <sub>1</sub> R <sub>3</sub>	Z	X	A	Y	n	Position of pyridine bond	According to Ex. No.	Yield %	M.p. °C.	Analysis data (theoretical and found values)			
											C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S	N %	S %	
3	H	CH	NH	—	S	2	2	1	80	75—77	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S	16.46	12.55	
	H									(255.34)		16.18	13.05	
										198—201	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	12.80	9.76	
										(328.27)		12.43	9.27	
4	H	N	NH	—	S	2	2	1	85	182—185	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S.3HCl	15.32	8.77	
	H									(365.73)		15.45	8.86	
5	—CH <sub>3</sub>	CH	NH	—	S	2	2	1	72	45—47	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S	15.60	11.91	
	6—								2	85	(269.37)		15.54	11.89
	—H									188—193	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	12.28	9.36	
										(342.30)		12.61	9.58	
5—	CH	NH	—	S	2	2	1	90	67—68	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S	14.83	11.31		
	—CH <sub>3</sub>									(283.40)		14.54	11.69	
6	6—									196—198	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	11.80	9.00	
	—CH <sub>3</sub>									(356.33)		12.05	9.08	
7	H	CH	NH	—	O	2	2	1	68	185—189	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O.2HCl	13.46	—	
	H									(312.21)		13.09	—	

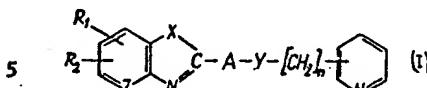
Ex. No.	R <sub>1</sub>	R <sub>2</sub>	Position of pyridine bond	According to Ex. No.	Yield %	M.p. °C.	Analysis data (theoretical and found values)		
							n	Ψ	Empirical formula (mol. weight)
8	H	H	S — S	1 4	2	75	85—87	$C_{13}H_{10}N_3S_2$	10.84 24.82
							(258.37)		10.27 25.18
							174—177	$C_{13}H_{10}N_2S_2 \cdot 2HCl$	9.45 19.36
							(311.30)		8.63 20.12
9	H	CH	S — S	3 3	2	68	134—135	$C_{16}H_{14}N_3S_2 \cdot 2HCl$	7.79 17.85
							(359.36)		7.91 18.01
10	H	CH	O — S	1 4	2	72	169—173	$C_{13}H_{10}N_2OS \cdot 2HCl$	8.89 10.17
							(315.23)		9.29 9.62
11	H	CH	NH — S	1 4	2	90	128—129	$C_{13}H_{11}N_3S$	17.42 13.28
							(241.32)		16.96 13.77
							180—183	$C_{13}H_{11}N_3S \cdot 2HCl$	13.37 10.20
							(314.25)		13.17 9.78
12	H	CH	NH — S	3 3	2	95	104—106	$C_{13}H_{10}N_3S \cdot 2HCl$	12.28 9.36
							(342.31)		11.71 9.33
13	H	CH	NH — S	1 2	2	80	148—150	$C_{13}H_{11}N_3S \cdot 2HCl$	13.37 10.20
							(314.25)		12.92 10.42
14	5-Cl-CH <sub>2</sub>	CH	NH — S	1 2	2	65	172—174	$C_{13}H_{10}ClN_3S \cdot 2HCl$	12.05 9.20
							(348.70)		12.23 9.62

Ex. No.	R <sub>1</sub>	R <sub>2</sub>	Z	X	A	Y	n	Position of pyridine bond	According to Ex. No.				Analysis data (theoretical and found values)		
									Ex. No.	Yield %	M.p. °C.	Empirical formula (mol. weight.)	N %	S %	
15	H	N	NH	—	S	1	2	2	68	175—177	C <sub>12</sub> H <sub>10</sub> N <sub>4</sub> S	23.12	13.23		
										(242.31)		22.99	13.00		
									191—194	C <sub>12</sub> H <sub>10</sub> N <sub>4</sub> S.3HCl	15.93	9.12			
										(351.70)		16.45	9.56		
16	H	N	NH	—	S	1	4	2	69	162—165	C <sub>12</sub> H <sub>10</sub> N <sub>4</sub> S.3HCl	15.93	9.12		
										(351.70)		15.98	9.06		
17	H	CH	NH	CH <sub>2</sub>	S	1	3	2	79	176—179	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	12.80	9.76		
										(328.27)		12.35	10.03		
18	H	CH	NH	—	S	1	3	2	93	182—185	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	13.37	10.20		
										(314.25)		12.55	10.39		
19	5—CH <sub>3</sub>	CH	NH	—	S	1	2	2	82	120—121	C <sub>16</sub> H <sub>16</sub> N <sub>3</sub> S	15.60	11.91		
										(269.37)		15.42	11.67		
	6— —CH <sub>3</sub>								198—200	C <sub>16</sub> H <sub>16</sub> N <sub>3</sub> S.2HCl	12.28	9.36			
										(342.30)		12.26	9.73		

Ex. No.	R <sub>1</sub>	R <sub>2</sub>	Z	X	A	Y	n	Position of Pyridine bond	Accoding Ex. No.	Yield %	M.P. °C.	Analysis data (theoretical and found values)		
												N %	S %	
5— 20	CH	NH	—	S	1	2	2	2	94	204—205	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub> S	19.57	11.20	
—NO <sub>2</sub>										(286.32)		19.17	10.86	
6—H										182—183	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub> S.2HCl	15.60	8.92	
										(359.25)		15.60	8.84	
5— 21	CH	NH	—	S	2	2	1	1	76	128—129	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> S	18.65	10.68	
—NO <sub>2</sub>										(300.34)		17.79	10.50	
6—H										188—189	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> S.2HCl	15.01	8.59	
										(373.27)		14.85	8.24	
22	H	CH	NH	—	O	1	2	2	65	164—168	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> S.2HCl	14.10	—	
										(298.18)		14.08	—	
5—Cl 23	CH	NH	—	S	1	3	2	2	70	160—165	C <sub>13</sub> H <sub>10</sub> ClN <sub>3</sub> S.2HCl	12.05	9.29	
6—H										(348.70)		11.90	9.00	
H— 24	CH	NH	—	O	1	3	2	2	85	177—179	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O.2HCl	14.10	—	
H—										(298.18)		14.42	—	
5— 25	CH	NH	—	S	1	4	2	2	76	82—84	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S	15.60	11.91	
—CH <sub>3</sub>										(269.37)		15.48	11.60	
6— —CH <sub>3</sub>										213—214	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> S.2HCl	12.28	9.36	
										(342.30)				

## WHAT WE CLAIM IS:—

1. Compounds having the general formula I and acid addition salts and quaternary ammonium derivatives thereof,



wherein

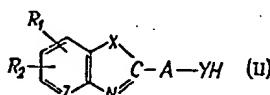
A stands for an alkylene group containing 1—5 carbon atoms or a valence bond; X stands for a —NH group or an oxygen

10 or sulphur atom; Y stands for a sulphur or oxygen atom; Z stands for a —CH— group or a nitrogen atom;

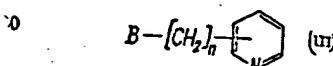
R<sub>1</sub> stands for a hydrogen atom or a methyl group;

15 R<sub>2</sub> stands for a hydrogen or chlorine atom or a —NO<sub>2</sub> or —CH<sub>3</sub> group; and n is an integer from 1 to 3.

20 2. A process for the preparation of compounds of general formula I and physiologically compatible acid addition salts and quaternary ammonium derivatives thereof, as claimed in claim 1, which comprises reacting an azole derivative having the general formula II



(wherein A, R<sub>1</sub>, R<sub>2</sub>, X, Y and Z are defined as in claim 1) with a pyridine derivative having the general formula III



35 (wherein B stands for an —NH<sub>2</sub> group or a halogen atom and n is defined as in claim 1) or with a salt thereof, and, if desired, transforming the obtained product in a known way to a physiologically compatible acid addition salt or a quaternary ammonium derivative.

40 3. A process as claimed in claim 2, which comprises using 2-(2-aminoethyl)-pyridine as the pyridine derivative of general formula III.

4. A process as claimed in claim 2 or claim 3, in which the reaction is carried out at a temperature of 100 to 150° C.

5. A process as claimed in any of claims 2 to 4, in which the pyridine derivative of general formula III or its salt is reacted in an amount equivalent to that of the azole derivative of general formula II.

6. A process as claimed in any of claims 2 to 5, wherein the reaction is carried out in the presence of an acid-binding agent.

7. A process as claimed in claim 6, wherein sodium hydroxide is used as the acid-binding agent.

8. A process for the preparation of compounds of general formula I as defined in claim 1 substantially as herein described with reference to the Examples.

9. Compounds of the general formula I as defined in claim 1 whenever prepared by a process as claimed in any of claims 2 to 8.

10. Azole derivatives and acid addition salts and quaternary ammonium derivatives thereof as herein described in the Examples.

11. Pharmaceutical compositions comprising as active ingredient at least one compound of general formula I as claimed in claim 1, or a physiologically acceptable salt or quaternary ammonium derivative thereof, in admixture with one or more pharmaceutical carriers and/or excipients.

12. Pharmaceutical compositions as claimed in claim 11 in the form of tablets, pills, coated pills, suppositories, capsules, solutions, emulsions, suspensions or injectable preparations.

13. Pharmaceutical compositions as claimed in claim 11 or claim 12, containing at least one other therapeutically active compound in addition to the azole derivative of general formula I.

14. Pharmaceutical compositions according to any of claims 11 to 13, substantially as herein described.

15. A process for the preparation of pharmaceutical compositions as claimed in any of claims 11, 12 and 14, which comprises admixing at least one compound of general formula I, as claimed in claim 1 or physiologically compatible salt or quaternary ammonium derivative thereof with one or more pharmaceutical carriers and/or excipients.

16. A process as claimed in claim 15 wherein at least one other therapeutically active compound is added to the composition.

17. Pharmaceutical compositions as herein described, whenever prepared by a process as claimed in claim 15 or claim 16.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.  
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